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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/288,719	04/09/99	KONTERMANN R	26083/201

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EXAMINER	
BECKERLEG,A	
ART UNIT	**PAPER NUMBER**
1632	22

DATE MAILED: 10/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/288,719	Applicant(s) KONTERMANN ET AL.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,23,25-29 and 83-86* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-18,23,25-29 and 83-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and response received on 7/23/01 has been entered. Claims 19-22, 24, 30-52, 54-71, 73-77, and 79-82 have been canceled. New claims 83-86 have been added. Claim 5 has been withdrawn from prosecution as being drawn to an invention non-elected with traverse in paper no. 20. Claims 1-4, 6-18, 23, 25-29, 53, 72, 78, and 83-86 are active and under prosecution in the instant application. An action on the merits follows.

The rejection of original, amended, or new claims 1-4, 6-18, 23, 25-29, 53, 72, 78, and 83-86 under 35 U.S.C. 112, first paragraph, is maintained in part over claims 1, 23, 72, 78, and 85-86. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that fusigenic peptide are described in DE19649645.4 which is almost identical to EP 0846772 which is written in english. However, mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky , 474 F.2d 671, 177 USPQ 144, (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific

portions of the referenced document where the subject matter being incorporated may be found. MPEP 608.01(p). Thus, the applicant's argument that fusigenic peptides are disclosed in the specification by virtue of reference to DE19649645.4 is unpersuasive as the reference to DE19649645.4 is improper. The applicant is reminded that the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In regards to the use of the disclosed single chain binding molecules as pharmaceutical agents for the treatment of disease, the applicant argues that Nettelbeck provides actual data demonstrating the targeting of an adenovirus capsid to the endothelial surface protein endoglin. Nettelbeck et al. discloses in vitro experiments which demonstrate the targeting of an adenovirus capsid to the endothelial surface protein endoglin using a bispecific diabody wherein the bound adenovirus was internalized into the cell. However, a nexus cannot be drawn between the in vitro data disclosed by Nettelbeck et al. and the treatment of any disease because the conditions under which binding and targeting occur in vitro differ substantially from those in vivo, and further, because Nettelbeck does not teach the level of target cell transfection of therapeutic gene

expression necessary to achieve any therapeutic effect on any symptom of any disease or condition in any mammal. The previous office action explained that the specification does not provide an enabling disclosure for the treatment or prophylaxis of any disease including cancer by administering any and all single chain binding molecules with a first specificity for the cell surface of a target cell, such as a tumor cell, and second specificity for a vector by any route of administration. The claims do not recite the administration of a vector. It is unclear in the absence of vector administration what possible therapeutic effect the single chain binding molecule itself could have on the target tumor cell. As discussed in detail above, the specification fails to provide an adequate description for making single chain binding molecules which bind to both a cell surface target molecule and a vector. The specification further fails to provide any guidance as to routes and methods of administration of vector and single chain binding molecule such that a therapeutic effect on a target cell is observed. The specification does not disclose whether the vector and single chain binding molecule are prebound *in vitro* prior to administration to the host or whether the single chain binding molecule is expected to encounter and bind both vector present at any location in the host and a target cell which may be present at a site distal from that of the vector. Further, the therapeutic potential of any compound *in vivo* is significantly affected by the physiological conditions at the site of administration, i.e. oral versus subcutaneous, the rate of clearance of the compound, i.e. subcutaneous versus intravenous, and the half-life and stability of the compound under physiological conditions. The specification does not provide any guidance as to any of these aspects of therapeutic gene or protein delivery. Finally, the specification

provides no guidance as to the nature of the gene(s) encoded by the targeted vector which are to have a therapeutic effect or teach the level of target cell transfection and expression of the encoded gene that would have any effect on tumor formation or tumor growth.

At the time of filing , the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). The specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to any particular cell type or to tumors or cells expressing tumor antigens in particular. The teachings of Nettelbeck et al. do not overcome these issues. Further, the applicant has not provided any specific arguments regarding the teachings of Deonarian and Miller or provided any evidence or in vivo targeted gene delivery or treatment of disease.

Therefore, in view of the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the time of filing, the absence of guidance provided by the specification for any of the conditions and parameters under which a therapeutic effect on cancer could be achieved *in vivo* using the disclosed single chain binding molecules with dual specificity for a vector and a target cell, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to prevent or treat cancer or any other disease or condition according to the instant invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-18, 23, 25-29, 53, 72, 78, and 83-86 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification discloses the construction of single chain binding molecules comprising a variable domain of a heavy chain of an immunoglobulin (VH) with a first specificity (A), a variable domain of a light chain of an immunoglobulin (VL) with a first specificity (A),a variable domain of a heavy chain of an

immunoglobulin (VH) with a first specificity (B), a variable domain of a light chain of an immunoglobulin (VL) with a first specificity (B), wherein the VH and VL domains are connected in the form of a VH-VL construct or VL-VH construct, and wherein the two VH-VL constructs are connected via a peptide (P). The specification further discloses that the first specificity (A) can be towards the cell surface of a target cell, such as a cancer cell, and the second specificity (B) can be towards a vector. The specification does not disclose or provide any written description for any VH-VL construct or antibody that binds to any type of vector, viral or plasmid. The specification does not identify any particular antibodies which recognize any DNA or RNA plasmid or any viral component, or describe any physical or chemical characteristic of VH or VL nucleic acid or amino acid sequences which recognize any viral or plasmid vector. Thus, of the enormous number of possible VH and VL amino acid sequences and nucleic acid sequences encompassed by the claims, the specification lacks written description for the identity and the sequences of any antibody or VH-VL fragment which is capable of binding a viral or plasmid vector with sufficient affinity to be useful for making a diabody according to the instant invention. *Vas-Cath Inc. V. Mahurkar,* 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of 'written description' inquiry, whatever is claimed" (see page 1117). By failing to identify or describe any antibody or VH or VL sequences specific for a viral or plasmid vector, the specification does not "clearly allow persons or ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath*

at page 1116). Adequate written description requires more than a mere statement that an element is part of the invention. The sequence itself is required. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the encompassed VH and VL sequences, therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER